REMARKS

Claims 32-37 are pending in the instant application. Claims 32-37 have been rejected. Claim 32 has been amended. No new matter has been added by this amendment. Reconsideration is respectfully requested in light of the following remarks.

I. Rejection of Claims Under 35 U.S.C. §103

Claims 32-37 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Anand et al. (U.S. Patent No. 6,291,208) and Heath (U.S. 2002/0135722) in view of Maraskovsky et al. (U.S. Patent No. 6,497,876) and Smith et al. (U.S. Patent No. 6,509,313). It is acknowledged that the prior art primary references do not focus on the use of the described anti-CD40 antibody conjugates in the absence of adjuvants, that Anand et al. teach the use of antibody conjugates comprising antibodies that bind antigen presenting cells to deliver antigens to generate immunogenic compositions and Heath teaches the co-administration of a CD40 stimulating moiety as an adjuvant in combination with an antigen. The Examiner has added Maraskovsky et al. to provide additional teachings pertaining to the use of other cytokines along with antigen-pulsed dendritic cells to stimulate immune responses. It is noted by the Examiner that Heath indicates that the anti-CD40 antibody is an adjuvant in the disclosed system and Anand et al. teach that the recombinant conjugate when administered without an extrinsic adjuvant elicits good priming but fades after a while and needed to be boosted and therefore does not preclude the skilled artisan from applying adjuvants to boost immune responses, *e.g.*, the adjuvants of Maraskovsky et al. The Examiner has also cites Smith to support

the use of cytokines for activating immune responses in the absence of toxicity. It is suggested that given that teachings of Heath to provide anti-CD40 with antigen in composition form or as a conjugate and the teachings of Anand et al. to provide antigen with anti-antigen presenting cell/dendritic cell antibodies; it would have been obvious to one of ordinary skill in the art to administer the antigen in the context of such antigen-antibody conjugate with the immunostimulatory anti-CD40 antibodies to boost the immune response to a wide variety of desired antigens, including providing both components in the same composition as taught by Heath. The Examiner suggests that one would have been motivated to target professional antigen presenting cells such as dendritic cells and the immunostimulatory agonistic CD40 antibodies to enhance the immune response to a wide variety of antigens. It is suggested that both Maraskovsky et al. and Smith teach cytokines as adjuvants for boosting immune responses. Applicants respectfully disagree with this rejection.

At the outset, while the Examiner suggests that Applicants cannot show nonobviousness by attacking references individually, it is respectfully pointed out that each reference as a whole must be considered in determining the motivation to combine the teachings therein and where the teachings of the prior art conflict, the suggestive power of each reference must be considered. MPEP 2143.01.

"There are three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art." *In re Rouffet,* 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998) (The combination of the

references taught every element of the claimed invention, however without a motivation to combine, a rejection based on a *prima facie* case of obvious was held improper.). The level of skill in the art cannot be relied upon to provide the suggestion to combine references. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999). MPEP 2143.01.

Applicants respectfully maintain that the motivation to combine the cited references is simply lacking because Anand et al. expressly teach that the disclosed conjugate antibody

> "enhanced immune response to an antigen without the use of an adjuvant" [emphasis added](column 3, lines 3-5),

wherein

> "strong adjuvant-independent serological responses to a delivered antigen can be obtained with conjugates formed with dendritic cell-specific monoclonal antibody and $CD4^+$ cell-specific monoclonal antibody." [emphasis added] Column 6, lines 48-51.

By way of example, Anand et al. show that

> "The recombinant conjugate, when administered to macaques without extrinsic adjuvant (e.g. alum or syntax), elicits good priming immune response, as measured by IgG titres to the peptide antigen on the conjugate. This response is also directed towards the native antigen as measured by recombinant P24 reactivity. The priming response fades after a while but was boosted in two out of three animals by anther does of the chimeric mab conjugate in PBS." [emphasis added] Column 8, lines 42-51.

Anand et al. conclude that

> "The experimental data presented herein and detailed below, demonstrates the enhancement of immune response to a peptide antigen in the absence of conventional adjuvants, by coupling to an anti-class II chimeric antibody." [emphasis added] Column 8, lines 52-55.

It is quite apparent from these passages and the Summary of the Disclosure at column 17, lines 57-67, that the whole of this disclosure teaches that a strong prime and boost immune response to an antigen can be obtained in the absence of ANY adjuvant including conventional adjuvants as well as adjuvants which modulate CD40. This is most telling in the section beginning at column 8, line 65, and ending at column 9, line 64, which describes "Vaccine Preparation and Use". Nowhere in this section of the patent disclosure do Applicants find a teaching or suggestion of vaccines containing adjuvants. Accordingly, there would simply be no motivation for one of skill to look to Heath, Maraskovsky et al., or Smith for an adjuvant for use with the antibody conjugate of Anand et al. because Anand et al. expressly discourages the use of adjuvants in combination with the disclosed antibody conjugate.

It is improper to combine references where the references teach away from their combination. *In re Grasselli*, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983) (The claimed catalyst which contained both iron and an alkali metal was not suggested by the combination of a reference which taught the interchangeability of antimony and alkali metal with the same beneficial result, combined with a reference expressly excluding antimony from, and adding iron to, a catalyst.). MPEP 2145.

Further, Applicants respectfully maintain that the mere suggestion of "co-entrapment" of a CD40 stimulating moiety with the appropriate T-cell independent and/or dependent antigen on or in a "carrier system" at paragraph [0026] is an insufficient disclosure for implying the use of an antibody that specifically binds to a molecule expressed by an APC. An antibody is generally

not considered a "carrier system" as the term "system", in particular, is "a regularly interacting or interdependent group of items forming a unified whole" (see The Merriam-Webster Dictionary definition enclosed herewith). It is unclear to Applicants how a group of interacting items forming a unified whole can be construed as an antibody. Based upon these limited teachings, there is nothing in this disclosure that would have provided the motivation to use an antibody that specifically binds to a molecule expressed by an APC in combination with an antigen and a CD40 stimulating moiety. Applicants maintain that there is little basis or motivation to combine the CD40 ligand adjuvant of Heath with the antibody conjugate of Anand et al., because Anand et al. expressly teach the omission of adjuvants for stimulating an immune response and Heath simply fails to suggest the use of an antibody to target an antigen to an APC.

Further, in addition to the lack of disclosure by Anand et al. for using ANY adjuvant, Heath expressly discloses that an adjuvant of the vaccines disclosed therein includes "reference to any string of amino acids or ligand which is selected so as to bind to at least a part of CD40" (see paragraph [0034]), wherein this includes an antibody "which is adapted to bind to said CD40" (see paragraph [0030]). Moreover, while Heath teaches the addition of at least one cytokine to the disclosed vaccine (see paragraph [0056]), this reference teaches that cytokines induce proliferation of B-cells and isotype switching (see paragraphs [0014]). This action of cytokines is further supported by the teachings of Maraskovsky et al. and Smith. As such, the cited prior art references of Heath, Maraskovsky et al. and Smith do not teach or suggest the conventional adjuvants used in the

context of the present invention, namely molecules that "induce a cytotoxic T lymphocyte response to the particular antigen". See page 13, lines 21-22. Accordingly, as supported by this disclosure at page 13, Applicants have amended claim 32 in an earnest effort to clarify the nature of the adjuvant of the present method.

In light of this amendment and the failure of the cited references to provide the necessary motivation to combine the teachings therein, these references cannot be held to make the present invention obvious under 35 U.S.C. 103(a). It is therefore respectfully requested that this rejection be reconsidered and withdrawn.

II. Conclusion

The Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

Jane Massey Licata

Jane Massey Licata
Registration No. 32,257

Date: **July 6, 2006**

Licata & Tyrrell P.C.
66 E. Main Street
Marlton, New Jersey 08053

(856) 810-1515

Merriam-Webster Online Dictionary

Thesaurus

system

51 entries found for **system**. The first 10 are listed below. To select an entry, click on it. For more results, click here.

Go

system
ABO system
autonomic nervous system
Bertillon system
binary star
block system

Main Entry: **sys·tem**
Pronunciation: 'sis-t&m
Function: *noun*
Etymology: Late Latin *systemat-, systema,* from Greek *systEmat-, systEma,* from *synistanai* to combine, from *syn-* + *histanai* to cause to stand -- more at STAND

1 : a regularly interacting or interdependent group of items forming a unified whole <a number *system*>: as **a** (1) **:** a group of interacting bodies under the influence of related forces <a gravitational *system*> (2) **:** an assemblage of substances that is in or tends to equilibrium <a thermodynamic *system*> **b** (1) **:** a group of body organs that together perform one or more vital functions <the digestive *system*> (2) **:** the body considered as a functional unit **c :** a group of related natural objects or forces <a river *system*> **d :** a group of devices or artificial objects or an organization forming a network especially for distributing something or serving a common purpose <a telephone *system*> <a heating *system*> <a highway *system*> <a data processing *system*> **e :** a major division of rocks usually larger than a series and including all formed during a period or era **f :** a form of social, economic, or political organization or practice <the capitalist *system*>

2 : an organized set of doctrines, ideas, or principles usually intended to explain the arrangement or working of a systematic whole <the Newtonian *system* of mechanics>

3 a : an organized or established procedure <the touch *system* of typing> **b :** a manner of classifying, symbolizing, or schematizing <a taxonomic *system*> <the decimal *system*>
4 : harmonious arrangement or pattern **:** **ORDER** <bring *system* out of confusion -- Ellen Glasgow>
5 : an organized society or social situation regarded as stultifying **:** **ESTABLISHMENT** 2 -- usually used with *the*
synonym see METHOD
- sys·tem·less /-l&s/ *adjective*

Pronunciation Symbols

Products Premium Services Company Info Contact Us Advertising Info Privacy Policy